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Heparin Induced Thrombocytopenia (HIT)

Heparin is a widely administered for the prevention and treatment of venous and arterial thromboembolism. Clinicians who prescribe heparin must be prepared to monitor for potential adverse effects; one of the most important of these is an immunoglobulin-mediated reaction, heparin induced thrombocytopenia (HIT).
In this brief review all issues related to "HIT' could not be addressed, therefore the emphasis would be on the important ones.

Clinical Features: HIT (sometimes known as HIT type II, or immune HIT) is characterized by thrombocytopenia usually beginning 5-10 days after the start of therapy. Its importance is related to its paradoxical high risk of thromboembolic events, like peripheral arterial occlusion, acute MI, stroke and death. In addition DVT and pulmonary embolism are strongly associated with HIT. Other thrombotic manifestations are adrenal hemorrhagic necrosis leading to hemorrhagic infarction, dural sinus thrombosis and venous limb gangrene.

The frequency of HIT is 1-3% in patients receiving unfractioned heparin for 1-2 weeks respectively. Typically the platelet count begins to decrease after 5-10 days after starting therapy (first day = day zero). It usually decreases by 50% and rarely reaches 10-20 x 10 exp 3/mm. Usually the count does not recover unless heparin is discontinued, after which it returns to normal in 4 days in 50% patients and 7 days in 90%, but occasionally requires several weeks for recovery. Of interest, bleeding complications are rare despite low platelet count and anticoagulation therapy. The disorder can be triggered by any route or dosage of heparin, including the flushes administered to maintain patency of IV catheters.

Treatment: Conventionally treatment of HIT requires immediate discontinuation of heparin by any route or in any dosage.
Warfarin: The role is controversial, since this agent is found associated with the unusual syndrome of venous limb gangrene in patients with HIT complicated by DVT.
LMWH: These drugs are considered contraindicated in HIT due to cross-reactivity (with unfractioned heparin UFH), high risk of triggering persistent or recurrent thrombocytopenia with associated thrombosis, and because other effective treatment options are available. Of interest, it should be noted that LMWH are less immunogenic than UFH, it is possible that wider use of LMWH in place of UFH will reduce the risk of HIT.
Treatment Adjuncts: Procedures like limb saving thrombectomy or embolectomy and insertion of vena caval filters to prevent pulmonary embolism may be considered. Thrombolytic therapy can be effective in selected patients. Aspirin and other antiplatelet agents have a modest indication and should not be primary therapy.
Limited experience suggest that plasma pheresis might work particularly HIT patients with DIC (disseminated intravascular coagulation).

Newer Treatment Strategies;

Recombinant Hirudin; Since no structural similarity with heparin, cross-reactivity is not a problem. Its effects can be easily monitored by aPTT (target value 1.5-3 times median of normal range).

Argatroban; A selective antithrombin excreted normally in patients with renal failure and may therefore be useful in patients with HIT receiving hemodialysis.

Danaparoid; A safe and effective agent in patients on hemodialysis with an advantage of single IV predialysis injection. Safely used in pregnant patient.

Salwa Ahsan (Staff Pharmacist)

Reference: Pharmacotherpy, vol 19, iss 2 yr 1999

Antibiotics and Dialysis

Antibiotics may be called as life saving agents depending upon the case we are dealing with. Many times the course of disease is complicated by renal failure and the need of dialysis. In such a scenario in which antibiotics are needed along with dialysis, one has to keep in mind the capability of the drug for being dialyzed. For drug, which is removed by dialysis, a supplemental doses is needed in order to maintain the therapeutic blood levels. Following list would be help full for optimizing dose of commonly used antibiotics in patients undergoing hemodialysis.

Antibiotics	Dialyzable	Supplemental Dose (AD)*
Ampicillin	Y	500-1000 mg
**Augmentin	Y	Oral = 375-625 mg IV = 0.6-1.2 gm
Amikacin	Y	2/3rd of the normal dose
Aztreonam	Y	500 mg
Amphotericin B	N	-
Acyclovir	Y	60-100% of low normal dose
Cefazolin	Y	2 gm
Cefixime	N	-
Ceftazidime	Y	1 gm
Ceftriaxone	Y	1 gm
Cefotaxime	Y	1 gm
Cefepime	Y	Initial dose or 250 mg
Cephalexin	Y	500 mg
Ciprofloxacin	Y	250-500 mg
Co-trimoxazole	Y	50 % of maintenance dose
Clarithromycin	Y	50 % of maintenance dose
Fluconazole	Y	100 mg
Gentamycin	Y	1-1.7 mg/kg
Levofloxacin	Y	250 mg
Meropenem	Y	500 mg
Ofloxacin	Y	100 mg
Quinine	Y	15 mg/kg Q12 hrly on day of dialysis
Streptomycin	Y	1/2 of normal dose
**Tazocin	Y	0.75 gm
Vancomycin	N	-

**After Dialysis* ***Brand names (combination product)* *Y = YES* *N = NO*

For drugs, which are removed by dialysis, need supplement dose after dialysis in order to compensate the lost amount. If dialysis session is near to the dose timing, one can hold the dose and give after dialysis; this will save cost of supplemental dose.

Salwa Ahsan (Staff Pharmacist)

Management of *Helicobacter pylori* Infection

The bacterium ***Helicobacter*** *pylori* can infect the stomach during childhood and cause lifelong chronic gastritis, which can lead to peptic ulcer disease. Curing *H pylori* infection cures ulcer disease. And since reinfection in adults is extremely rare, adequate treatment permanently cures this former chronic recurrent, serious disease. If ulcers do not recur neither do ulcer perforation or bleeding; quality of life increases, sick leave decreases, and less money is spent on visiting the doctor and drugs.

Selecting a regimen: An evidence based choice of treatment is impossible because we lack large randomized trials comparing the highly effective regimens. Treatment of *H pylori* is difficult because of the rapid development of resistance to antibiotics, especially to metronidazole, which occurs more commonly in women and patients from developing countries because of previous treatment for gynecological infections or infective diarrheas. Resistance to clarithromycin may occur after failed treatment or after use of this drug for other indications such as respiratory tract infections. Dual treatment with proton pump inhibitors is now obsolete due to lack of efficacy. Several triple or quadruple therapies have been sufficiently investigated and seem to be able to cure either 80% (intention to treat) or 90% (per protocol) of patients. The table shows currently useful treatments, but none has surfaced as the final treatment of choice. Metronidazole and clarithromycin are the two key antibiotics. Antibiotic resistance against these two drugs, either primary or induced after treatment, is clinically important.

Regimen based on Clarithromycin

Length of treatment	Component Drugs
7-10 days	PPI* bid + Amoxicillin 1 gm twice daily + Clarithromycin 500 mg twice daily

Regimen based on Metronidazole

Length of treatment	Component Drugs
7-10 days	PPI* bid + Amoxicillin 500 mg 2-3 times daily + Metronidazole 400 mg twice daily

First Line treatment:
If metronidazole resistance is likely a proton pump inhibitor in combination with amoxicillin and clarithromycin given for one week is preferable.

Second line treatment:
After a proved failure with a treatment containing metronidazole, a patient is likely to be colonized by a resistant strain of *H pylori*. In this case a proton pump inhibitor should be given in combination with amoxicillin and clarithromycin for a week, with about 90% success. If *H pylori* eradication is unsuccessful after a treatment containing clarithromycin and the patient is likely to harbour a metronidazole resistant strain of *H pylori*, then either omeprazole in combination with amoxicillin and metronidazole or quadruple therapy (PPI* bid + Colloidal Bismuth Citrate 120 mg qid + Tetracycline 500 mg Q6H + Metronidazole 400 mg Q6H) are the only logical options, with roughly 75% success. The regimens containing clarithromycin plus metronidazole should be disfavored as in case of treatment failure the back up plan options will be limited.

What to tell patients? There has been much discussion of *H pylori* in the media, and many patients are aware of its ulcerogenic and carcinogenic potential and may request antibacterial treatment if they are found to be infected. At present there is no evidence to suggest that screening and treating patients without risk factors will prevent gastric cancer. The risk of transmission to partners is low in adults, and treatment of the entire family is not warranted. Whatever treatment is chosen, patients need careful counseling. The reasons for embarking on the treatment and the importance of compliance despite possible side effects need to be emphasized, and the possible side effects must be carefully discussed. The need for good compliance needs special attention, as it is crucial to the success of treatment.

*PPI = Proton Pump Inhibitor (Omeprazole 20 mg bid)

Abdul Qadeer Sajid (Pharmacist)

References: BMJ vol. 323, Nov 2001. BMJ, vol 320, Jan 2000

Story of A Pharmacist In a Busy Pharmacy

A pharmacist, who was working alone in a busy hospital pharmacy, received a stat order for oral clonidine 1 mg and levodopa 125 mg for a growth hormone stimulation test on an 8year-old child.

Despite significant pressure from the stat order and a backlog of work, the pharmacist, who was unfamiliar with the test, took time to research the information and discovered that the correct test dose of clonidine for a pediatric patient was 0.15 mg/meter square.

After calling the physician, the order was changed to clonidine 0.1 mg. Unfortunately, even successful outcomes like this one may not be widely appreciated if productivity is sacrificed to enhance patient safety. Nevertheless, numerous errors reported through the USP-ISMP Medication Errors Reporting Program have resulted when practitioners felt significant pressure to place productivity above patient safety, especially when faced with inadequate staffing. Institute for Safe Medication Practices (ISMP).
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ACE inhibitor, diuretic and NSAID: a dangerous combination

The control of hypertension by ACE inhibitors and diuretics and their beneficial effects in heart failure are antagonised by NSAIDs. Concurrent use of NSAIDs and diuretics is associated with a twofold increase in the risk of hospitalisation for heart failure compared with diuretics alone.[1] Moreover, ACE inhibitors, NSAIDs and diuretics, individually or in combination, are involved in over 50% of cases of iatrogenic acute renal failure reported.

More specifically, the combined use of ACE inhibitors, diuretics and NSAIDs, termed the "triple whammy", is implicated in a significant number of reports of drug-induced renal failure.[2] This effect is also seen with COX-2 inhibitors and angiotensin receptor antagonists ("sartans").[3] In 2002, 28 of the 129 reports of acute renal failure implicated one of these combinations. Most reports of drug-induced renal failure relate to elderly patients, and this applies as well to renal failure associated with the triple therapy (median age 76 years). The fatality rate for cases of renal failure with the "triple whammy" is 10%.

The use of ACE inhibitors and angiotensin receptor antagonists is increasing, as is the use of these agents in combination products with a diuretic. Episodes of renal failure appear to be precipitated by mild stress (e.g. diarrhoea, dehydration) in a patient taking the triple combination or by the addition of a third drug (usually an NSAID) to the stable use of the other two.

It is therefore to remind prescribers that the combination of ACE inhibitors (or angiotensin receptor antagonists), diuretics and NSAIDs (including COX-2 inhibitors) should be avoided if possible, and great care should be taken with ACE inhibitors and NSAIDs in patients with renal impairment.

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